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Post-translational modifications of steroid receptors

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Abstract

The multiple physiological functions of steroid hormones have been known for many years. The cloning of the steroid receptors in the mid-1980s led to the concept of ligand-activated transcription factors and to the identification of specific DNA response elements in the regulatory regions of target genes. The next main development was the identification of cofactors with activating or repressing functions, of which several act by modifying histones and locally affecting the chromatin structure. Work from several groups shows that the steroid receptors themselves can also be modified at various positions. Besides the long-known phosphorylation at tyrosines and serine/threonine residues, other covalent additions such as acetylation, ubiquitylation and sumoylation have been evidenced for steroid receptors in recent years. These modifications affect receptor stability and activity, and provide potential mechanisms for cell- or gene-specific regulation. A better understanding of the impact of these post-translational modifications (PTMs) on steroid receptor function should help in the identification of novel ligands with improved clinical profiles.

Keywords: Steroid receptor; Phosphorylation; Acetylation; Ubiquitylation; Sumoylation

1. Introduction

The nuclear receptor super-family has 48 members in humans [1]. The steroid receptor sub-group is composed of the androgen receptor (AR), two estrogen receptors (ER) named ERα and ERβ, the progesterone receptor (PR), the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). Steroid receptors are mainly found, in the absence of hormone, in the cytoplasm complexed to chaperone proteins. Following ligand binding, they undergo conformational changes and move to the nucleus where they activate or repress target genes as homodimers. They are organised in four main domains [2]: an N-terminal region bearing important transactivation functions, a DNA-binding domain (DBD) composed of two zinc fingers, a hinge region harbouring the nuclear localisation signal and a ligand-binding domain (LBD) with additional transactivation functions. The LBD consists of 12 α-helices and undergoes extensive conformational changes following binding by the hormone. Most strikingly, the C-terminal α-helix folds over to close the hydrophobic pocket into which the ligand binds. This creates a platform for recognition by cofactors, a necessary step for the recruitment of the transcription machinery and the activation of target genes. Most DNA response elements recognised by steroid receptors are organised as semi-palindromic hexamers, but variant response elements have more recently been found [3,4]. Additional mechanisms such as tethering to other transcription factors and non-genomic effects have been described [5]. Also, repressive functions of steroid receptors on several target genes have been observed [6].

The transcriptional activity of steroid receptors is mainly governed by ligand binding but more and more studies document that post-translational modifications (PTMs) play an important additional part. In many cases, the exact modification sites and the modifying enzymes involved have been identified. These covalent changes may affect receptor stability, subcellular localisation as well as the interactions with other

Abbreviations: AR, androgen receptor; CDK, cyclin-dependent kinase; DBD, DNA-binding domain; ER, estrogen receptor; GR, glucocorticoid receptor; LBD, ligand-binding domain; MR, mineralocorticoid receptor; PR, progesterone receptor; PTM, post-translational modification.

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proteins. Interestingly, a regulatory cross-talk between some of these modifications has been evidenced, adding to the complexity of the system. This review gives a succinct overview of the impact of phosphorylation, acetylation, ubiquitylation and sumoylation on steroid receptor function.

2. Phosphorylation of steroid receptors

Steroid receptor phosphorylation has been studied for much longer than the other PTMs and a wealth of literature data, including extensive reviews, are available [7]. Only a few new interesting aspects will therefore be discussed here including recent results on the specific recruitment of cofactors by phosphorylated ERα. A schematic representation of conserved phosphorylation sites is shown Fig. 1.

2.1. AR phosphorylation

The existence of basal and regulated AR phosphorylation sites has been reported [8,9]. In one study S94 is found to be constitutively phosphorylated whereas S16, S81, S256, S308, S424 and S650 exhibit elevated phosphorylation following ligand binding [8]. Another group showed S650 phosphorylation to be constitutive and dependent on the phosphorylation of S515 [9]. There are conflicting data concerning the kinases involved but some studies suggest MAP kinases and Akt to play a role [10,11]. For instance, S213 and S791 are modified through activation of the Akt pathway, downstream of Her-2/neu. Interestingly, immunochemical analysis using a specific antibody showed phosphorylation at position S213 to be found in prostate epithelial but not stromal cells [12]. The fact that, according to one study, Akt-controlled phosphorylation can either impair or stimulate AR function in LNCaP cells dependent on passage number, makes conclusions about the in vivo role of AR phosphorylation difficult [13]. Phosphorylation does not seem to have a major impact on AR activity, despite the existence of multiple targeted sites. For instance, the S94A, S515A and S650A mutations do not affect AR function in cell-based assays [9]. More recently however, AR S650A was shown to have impaired activity, due to deficiency in nuclear export [10]. Also, dephosphorylation of the AR N-terminal domain by PP2A is accompanied by a loss of activity [14]. Finally, new experiments using peptide arrays suggest that

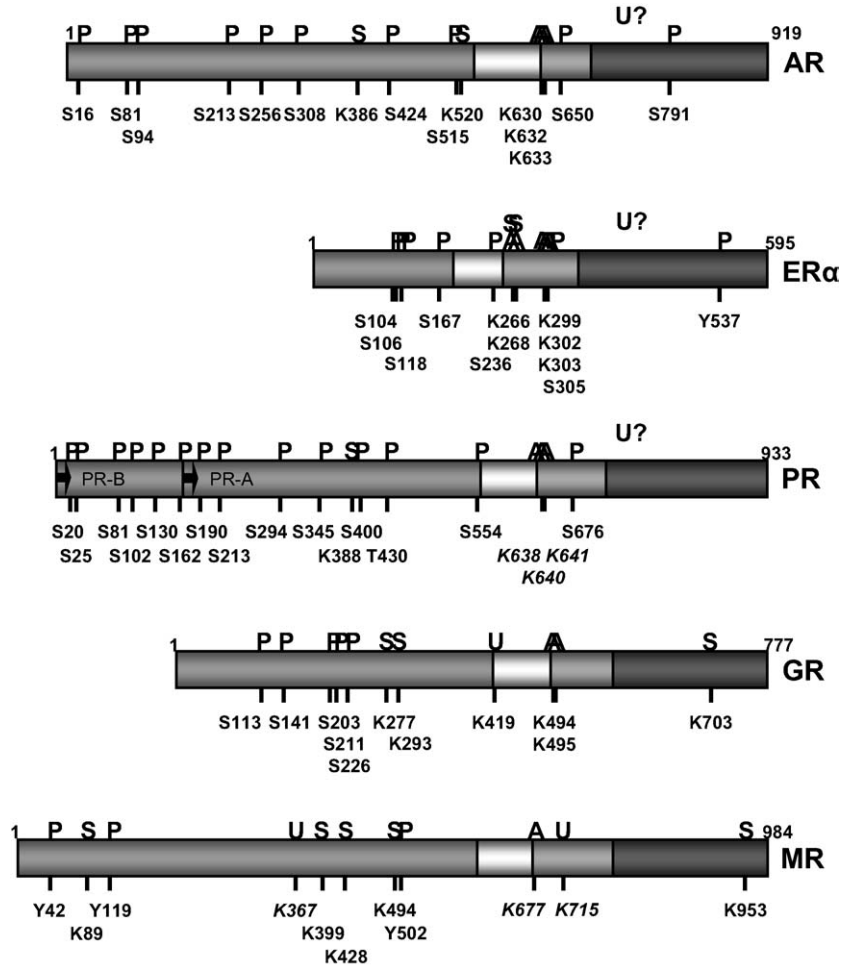

Fig. 1. Schematical representation of the human steroid receptors and location of their proven or potential PTM sites. Some of the positions were inferred from other species, due to the high conservation of the protein sequences, and are shown in italics. U? indicates that the exact ubiquitylation site has not been identified. P: phosphorylation; A: acetylation; U: ubiquitylation; S: sumoylation.